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April 17, 1945

Dear Michael:

Many thanks for sending the manuscript; we have read it with interest and consider it a valuable contribution to the C' literature. However, it would be less than honest not to admit that I read portions of the article with some distress, particularly the implications that we have thrown the complement components into a state of confusion and that much of our work is unsound. We feel that the field of complement, so arduously studied by many before us, is one in which much groping had to be done; for the field had growing pains, and errors both in technique and interpretation were bound to occur. All of us, including workers in both our laboratories, should be somewhat more generous in evaluating the other's work. If this were merely a protest it might sound whining, but the fact that we too have been working on improving the methods of component titrations as evidenced in the enclosed publication and in Seifter's thesis presented in May, 1944, causes us to feel hurt by the implications in Bier's article.

It should not be lost sight of that in our paper I of the series we were led to studying mutual substitutiveness by Hegedus and Greiner's work, and it still is true that the methods that they used, despite correct principles, could result in incorrect conclusions. The article by your group also calls attention to this, the fact that anticomplementary effects as between the species' C' fractions can occur. Then too it should not be forgot that we used the word effectively in describing the failure of mutual substitution, and as regards the fractions we used and some H. & G. used this still holds true. Finally, you should recall that in your first hu C' paper you used R (reagent) sera for testing, the C' component content of which you had not determined. A case in point was your use of fixed gp serum as a reagent, which, after all, was one of the principle issues under discussion in our paper I. Then also, we think a re-reading of the last paragraph preceding the summary of our paper I contains some pertinent cautions which should have earned us some consideration from Bier. We do not believe that any mistakes we made, and we have made them, have set back progress on C' any more than we believe the natural assumption on your part that C'1 was the only combining component of C', and therefore the basis for a quantitative absolute method for C' determination, has set back progress. On the contrary we think that the mistakes of both our groups have stimulated us to further research on a higher level, and perhaps to further mistakes.

At any rate, to get back to the paper, we do agree with Bier and your group that the principles laid down by H. and G. are sound, although with your group we do not agree that these authors applied them consistently. By the way, all of us should be aware that the foundation for much of the work on C' component titrations

can be found in the studies of DaCosta Cruz and Penna, countrymen of Dr. Bier's, reported in vol. 104 of the CR Soc de Biol., and we suggest that these authors be mentioned in the bibliography of the paper.

I should like you to read the review article which is enclosed if you have not already done so, paying particular note to sections which are marked. As you will note this paper was submitted for publication before I saw you, and further was reported on at the AAAS meetings in Cleveland by Seifter last September.. Also, I should appreciate your reading of sections 8,9,10, and 11 of Seifter's thesis, a copy of which is enclosed. Much of this thesis, we hope you bear in mind, proposed further work which has since been carried out and has caused us in turn to revise further some of the ideas on component concentrations. This in turn has caused us to reconsider some of the ideas of complement fixation as you will note in the thesis chapter devoted to that subject, and in a paper (also enclosed) published in July, 1944. In this latter paper the last paragraph on page 39 is pertinent to the discussion, in that it shows that we had already begun to project the conception of the relation of the original concentration of a particular component to the order in which it was fixed.

In the thesis you will note that we had further developed the method of titer at the initial point level, on the basis of which we found the concentrations of C'1 and C'4 in human complement to be about 9 times effective in the hemolytic system than C'3 and C'2. Considering the variations of individual sera, and the slight differences in our methods, this is excellent agreement with Bier's results which show the former group of components to be about 12 or so times in greater concentration in hu serum than C'3 and C'2. In this respect, our published review article gives the order of concentration of the C' components and in our estimation deserves some reference in Bier's paper -- not so much as a matter of establishing priority but as a demonstration that some of our work is capable of confirmation.

About a year ago we completed a study of approximately 300 cases of infections in humans in which we followed the titer of each C' component by the method of specific reactivation at the initial point titer level, as outlined in Seifter's thesis. This work was reported on at the AAAS meetings in September and was summarized in the review article.

In view of these facts, we wonder if we justly deserve the intimated opprobrium offered by Dr. Bier, in particular since our work on diseased sera will shortly be submitted for publication, and will be looked upon with doubt if these implications stand. This would be unfortunate precisely because the work is based on a method of titration closely similar to Bier's method.

I think it unfortunate that the submitted article went to press without Bier's and your knowledge of our work of the past two years.

We have been too occupied to prepare it for publication other than in the review article.

Looking back to three and four years ago, it is obvious that all of us nurtured certain misconceptions about the components of complement, and the development of knowledge about the components will not best be served by encouraging strong doubts as to the validity of the future work of either of our laboratories. I think it is fortunate that we can frankly discuss these matters by letter instead of burdening the journals with wearying polemics.

I have not pulled punches in this letter because on another occasion when you read our fixation paper (previous to publication) you likewise did not hold back strong criticism, for which we were grateful to you and on the basis of which we made certain adjustments.


With best wishes and regards,

Sincerely yours,



E.E. Ecker.

P.S.

The paper on substitution now in press in the Proceedings is by Ecker and Pillemer. Pillemer is back with me but works on other problems. 

If you care to show this letter to the other authors 